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Hemosiderosis With Diabetes Mellitus in Untransfused Hemoglobin H Disease

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A 37-year-old untransfused, non-drinking man with Hemoglobin H-CS disease presented with insulin-dependent diabetes mellitus, markedly elevated serum ferritin level, and marked iron deposition in hepatocytes. He did not carry either of the two common mutations of the HLA-H gene for hereditary hemochromatosis, namely, Cys282Tyr and His68Asp, nor did he have the associated HLA marker (HLA-A3, B7 nor B-14) for the disease. Patient with HbH disease should be monitored for iron overload. Am. J. Hematol. 57:160–163, 1998.

Key words: HbH-CS; hemosiderosis; diabetes mellitus

INTRODUCTION

In Hemoglobin H (HbH) disease, usually three of the four α goblin genes are deleted and patients present with thalassemia intermedia. Occasionally, patients have deletion of two α globin genes together with the α globin gene mutant, hemoglobin Constant Spring (HbH-CS) [1]. The latter is associated with a variable degree of anemia, which may be more severe than classical HbH disease [2]. Iron absorption studies have demonstrated an increased absorption in thalassemic patients with ineffective erythropoiesis and erythroid hyperplasia [3]. While iron overload may occur late in the course of HbH disease [4], it is rare in young untransfused subjects. Here we describe a young untransfused HbH-CS patient with iron overload and insulin-dependent diabetes mellitus.

CASE REPORT

A 37-year-old man presented in January 1995 with left hypochondrial pain for 3 days after lifting heaving objects. Twelve years ago, he was accidentally found to have anemia and splenomegaly but later defaulted follow-up. He claimed to have no symptoms of anemia until this presentation and had no previous blood transfusion. He had not taken any oral iron and was not an alcohol drinker. He was married with one child. His elder brother died in his thirties because of a febrile illness, but there was no family history of anemia nor diabetes mellitus. Physical examination revealed pallor, hyperpigmentation of skin, mild jaundice, hepatomegaly of 6 cm below right costal margin, and splenomegaly of 28 cm below left costal margin. There were no thalassemic faces. Investigations showed Hb of 8.0 g/dl (NR: 13–18 g/dl), red cell count 3.6×10^{12}/L (NR: 4.5–6.5 $\times 10^{12}$/L), hematocrit 31.9% (NR: 40–54%), MCV 88.6 fl (NR: 76–96 fl), MCH 22.3 pg (NR: 27–32 pg), MCHC 25.2 g/dl (NR: 30–36 g/dl), reticulocyte count 8.9% (NR: 0.2–2.0%), white cell count 4.64×10^9/L, platelet count 147×10^9/L (NR: 150–400 $\times 10^9$/L). Hb pattern and iso-electrofocusing showed Hb A 75.4%, Hb A_2 0.6% (NR: 2.3–3.5%), Hb F 2.1%, Hb H 18.6%, Hb Barts 1.2%, and Hb CS 2.1%. Bone marrow biopsy showed marked erythroid hyperplasia with poor hemoglobinization. DNA was extracted from peripheral blood leukocytes and the ζ gene map of the patient obtained as described previously [5], was compatible with α thalassemia 1 (α thal 1, SEA) genotype. In addition, polymerase chain reaction (PCR) amplification of the α2 gene [6] and digestion of the 1085 base pair (bp) α2 gene fragment with Mse I gave only two fragments (Fig. 1), 562 and 523 bp, respectively, as compared to three fragments of 523, 401, and 161 bp in the normal subject. This is in keeping with a Constant Spring mutation at the termination codon (UAA → CAA). PCR amplification of the β gene was made and screening for the twelve common Chinese β gene muta-

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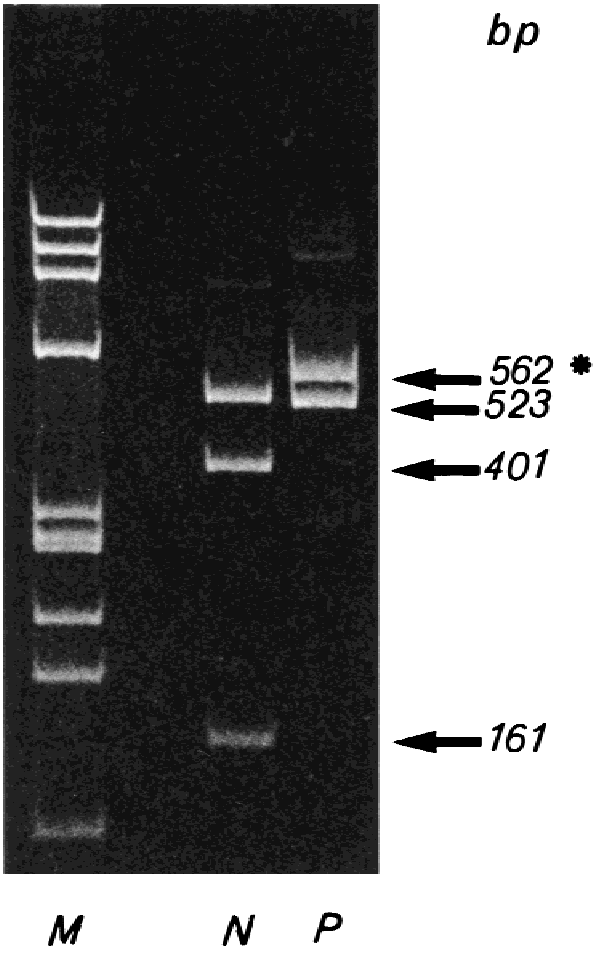

Fig. 1. Mse I digest of a PCR amplified α2 gene fragment. The Constant Spring mutation abolished an enzyme site, giving two fragments (562 and 523 bp) in the patient (P) vs. three fragments (523, 401, 161 bp) in the normal control (N). M = molecular weight marker that is a ϕX 174/Hae III digest.

tions using a reverse dot blot, allele specific hybridisation technique was negative [7]. The two common mutations, Cys282Tyr and His68Asp, of the HLA-H gene for hereditary hemochromatosis were screened using specific PCR primers for amplifications as described by Feder et al. [8], followed by direct restriction enzyme analysis with either SnaB I or Mbo I respectively [9]. DNA of the patient was negative for both of these mutations. Liver function test showed bilirubin 34.5 mg/L (NR: 1.75–13.45 mg/L), alanine transaminase 113 μ/L (NR: 7–41 μ/L), normal alkaline phosphatase and aspartate aminotransferase. Lactate dehydrogenase was 690 μ/L (NR: 200–360 μ/L). Serum iron was 167.6 μg/L (NR: 391–1,731 μg/L) and ferritin was 6,582 μg/L (NR: 10–300 μg/L). Spot blood glucose was 75.7 mg/dl. Hepatitis B surface antigen and hepatitis C virus serology were negative. Echocardiography showed that resting ejection fraction of the left ventricle was 61%. Computed tomography of the abdomen showed hepatosplenomegaly with increase in density of the liver compatible with hemochromatosis. He was started on subcutaneous desferrioxamine 2 g daily, three times a week, but compliance was poor. In May 1995 he had splenectomy for symptomatic splenomegaly, cholecystectomy for gallstones, and wedge liver biopsy performed intraoperatively for tissue iron status showed heavy deposition of iron mainly in the hepatocytes associated with fibrosis. On discharge, he was put on penicillin prophylaxis, folic acid, subcutaneous desferrioxamine 2 g daily 3 times per week, and vitamin C. Hb was stable at 10–11 g/L post-splenectomy. In March 1996 he presented with weight loss, malaise, polydipsia, polyuria, nausea, and vomiting. Blood glucose was 684.8 mg/dl, urine ketone 3+, arterial blood pH 7.36, and ferritin 16,000 μg/L. He was treated with intravenous fluid and insulin. Endocrine investigation showed that thyroxine, luteinising hormone, follicule stimulating hormone, testosterone, parathyroid hormone, and cortisol levels were within normal limits. Magnetic resonance imaging (MRI) scan of the abdomen showed hepatomegaly with gross hemosiderosis in the liver and pancreas (Fig. 2). HLA typing revealed that he was HLA-A11 and A11.2 and homozygous for B13.

DISCUSSION

This young, non-alcoholic patient with HbH-CS disease had severe iron overload as revealed by skin hyperpigmentation, increased serum iron and ferritin, impaired liver function test, insulin-dependent diabetes mellitus; and diffuse decrease in signal intensity in liver and spleen in the MRI scan films. This was also confirmed by increased tissue iron deposit on liver biopsy.

Ferrokinetic studies have shown that ineffective erythropoiesis and erythroid hyperplasia is associated with increased gastrointestinal absorption of iron [3]. Secondary hemosiderosis is well known to occur in severe forms of β-thalassemia and untransfused thalassemia intermedia but was thought to be unimportant in HbH disease [10]. An autopsy study has shown that tissue hemosiderosis was considerably less in HbH disease compared to β-thalassemia major and Hb E-thalassemia [11]. However, in HbH disease patients, male patients (21–45 years old) had a raised ferritin level ranging from 170–1,330 μg/L compared to age-matched normal controls (33–370 μ/L) [4]. Our patient, who had no anemic symptoms and no blood transfusion, presented with a very high ferritin level of 6,582 μg/L and hemosiderosis. Although iron overload occurs in untransfused thalassemia intermedia, hemosiderosis resulting in clinical disease is rare in untransfused HbH disease. In one series [12], clinical manifestations of hemochromatosis (hyperpigmentation and impaired liver function) were found to occur in transfused HbH patients who were alcoholic. However, these

Fig. 2. T2* weighted MRI scan film of the abdomen showing generalised decrease in signal intensity in the liver and pancreas (arrow) in keeping with gross iron overload in the liver and pancreas.

two risk factors (transfusion and alcohol drinking) were absent in our patient.

Hereditary hemochromatosis is transmitted as an HLA-linked autosomal recessive disorder with clinical disease developing in homozygous patient. The hemochromatosis gene is closely linked to HLA-A3, B7 and B14 [13]. In the Western population, the expression of HLA-A3 allele was observed in 29% of control subjects compared to 74% of patients with hereditary hemochromatosis [14]. Moreover, patients with thalassemia trait who had inherited this HLA-haplotype, have also been found to have clinically significant hemosiderosis [15]. HLA-A3, B7, and B14 are, however, absent in our patient. Nonetheless, it does not exclude the possibility that the hemochromatosis gene is linked to a different HLA allele in the Oriental population. This patient did not have either of the two common mutations in the HLA-H gene described in Caucasians [8,9], but does not exclude the fact that he may have a mutation elsewhere on the gene. In our population, primary hemochromatosis is extremely rare.

This patient has insulin-dependent diabetes mellitus. There is no family history of the disease. MRI scan has been shown to be a very sensitive method to define the body iron status [16]. The gross hemosiderosis in the pancreas was well demonstrated in the T2* weighted films of the MRI scan and the hemosiderosis of the pancreas would account for the development of insulin-dependent diabetes. Moreover, severe iron overload resulting in diabetes mellitus in untransfused HbH disease has not been reported.

Previous studies [17,18] have demonstrated splenectomy might aggravate the state of iron overload. This may account for the rapid increase of the ferritin level from 6,582 to 16,000 μg/L.

In this patient, aggressive chelation therapy, close monitoring of cardiac function, repeat MRI of the liver, and serial monitoring of α-fetoprotein level for possible subsequent development of hepatocellular carcinoma are being carried out.

Our patient has severe iron overload, which is uncommon in young, untransfused patients with HbH disease. He is a non-drinker and there is no evidence that he carries the hemochromatosis gene. The only explanation for the hemochromatosis is erythroid hyperplasia in the bone marrow with ineffective erythropoiesis, resulting in increased iron absorption. This case illustrates that severe iron overload may occur in untransfused HbH disease and close monitoring of the iron status should be advocated, especially in the older patients, since HbH disease is usually associated with a normal life-span.

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